Amendments to the Drawings:

Submitted herewith are fifteen (15) sheets of Formal Drawings. These sheets include Figures 1-12. Please replace originally filed Figures 1-12 with the fifteen sheets of Formal Drawings (Figures 1-12) submitted herewith.

Enclosure: Fifteen Replacement Sheets of Figures 1-12

REMARKS / ARGUMENTS

A review of the file indicates that the application was filed with original claims 1-54. In the Supplemental Amendment dated February 25, 2002, Applicants cancelled claims 11-53 (should have been 11-54) and inadvertently added new claims "54 and 55," instead of new claims 55 and 56, respectively. In light of this error, Applicants have renumbered the claims herein, and all discussion with respect to claims "54 and 55" in the Office Action will be referred to hereinafter with the correct claim numbering of claims "55 and 56," respectively. As such, claims 1-10 and 55-56 are currently pending in this application, and claims 11-54 have been previously cancelled.

Claims 1-10 and 55-56 have been amended herein. No new matter has been added by way of this amendment, and support can be found throughout the specification. New claims 57-59 have been added. No new matter has been added by way of this amendment, and support can be found in the specification at pages 4-6, 9 and 20-23. Thus, following entry of this amendment, claims 1-10 and 55-59 will be pending.

Applicants respectfully request reconsideration of claims 1-10 and 55-59.

I. Objections to the Drawings

The Examiner has objected to the drawings because Figures 2-4 and 9-12 "are blurry and dark, thus hard to discern lanes" (Office Action, page 3). In addition, the Notice of Draftsperson's Patent Drawing Review indicates that certain figures are objected to because (a) the margins are not acceptable in Fig. 3; (b) the views are not labeled separately or properly in Figs. 5A - 12C; and (c) the numbers, letters and reference characters are not of the appropriate size in Fig. 5A - 6D.

Applicants are submitting herewith Replacement Sheets 1-15 containing Figures 1-12. Each of the replacement Figures rectifies the issues presented in the Notice of Draftsperson's Patent Drawing Review.

However, Applicants respectfully traverse the Examiner's objections relating the "blurry and dark" figures. Applicants respectfully submit that Figures 2-4 and 9-12 are clear. As the Examiner is aware, Western blots, and other types of blots and gels, inherently produce a somewhat "blurry" appearance. Notwithstanding, in Figure 2, for example, it can

be clearly shown that the addition of BMP induces Smad degradation (lane 3); whereas the addition of LLF (Leu-Leu-Phe, a proteosome inhibitor) blocks BMP-induced Smad degradation (*e.g.,* compare lanes 4 and 5 with lane 3). Similarly, Figure 3 clearly shows that the addition of LLF accumulated more high molecular weight, ubiquitinated Smad1 protein (compare lanes 3 and 5 with lanes 2 and 4). Likewise, Figure 4 plainly shows that WWP1.1 (a GST fusion protein with the first WW repeat) binds to Smad1 (lane 2) but not the Smad1 with a mutated PY motif (lane 3). These data in Figures 2-4 are entirely consistent with the discussion of these figures in Example 1 on pages 28-29. The same also holds true for each of the remaining figures objected to by the Examiner.

In view of the foregoing, Applicants respectfully submit that Figures 2-4 and 9-12 in the Drawings of the above-referenced application are not "dark and blurry" and comply with all of the requirements of 37 C.F.R. 1.121(d). Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

II. Objection to Claims 2-10 and 55-56.

Claims 2-10 and 55-56 have been amended to recite "The method according to claim..." instead of "A method according to claim...".

Claims 2, 4, 54 and 55 have been amended to recite the three letter amino acid code in place of the single letter amino acid code.

Claim 2 has been amended to correct the spelling of "ubiquitin."

Accordingly, reconsideration and withdrawal of these objections is respectfully requested.

III. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

1-10 and 55-56 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Applicants respectfully traverse this ground of rejection.

The Examiner admits that the speciation is enabling for methods using a HECT E3 ubiquitin ligase domain, but alleges that the specification does not provide enablement for

methods using variants or a polypeptide comprising a HECT E3 ubiquitin domain (Office Action, page 4). The Examiner opines that the specification and claims identify polypeptides comprising a HECT E3 ubiquitin ligase WW domain, but that "no conserved domains or structural characteristics are provided for the claimed variants thereof" and that a "skilled artisan would have to engage in undue experimentation to construct said variants and test [the] same for activity for the desired properties of the native proteins" (Office Action, page 5).

M.P.E.P. § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation," and "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

At the time the application was filed, it was routine for those skilled in the art to prepare and screen large numbers of polypeptide variants, (*e.g.*, high-throroughput screening assays for functional activity), and, contrary to the Examiner's assertions, Applicants submit that one of ordinary skill in the art would know how to identify and utilize other HECT E3 ubiquitin ligase domains, or variants thereof, without undue experimentation. This is especially true in light of the knowledge of those skilled in the art in combination with the extensive guidance provided by the specification.

For example, the specification defines what constitutes a "HECT E3 WW domain," and includes a number of embodiments:

> A HECT E3 WW domain, as used herein, is a region of a HECT E3 ubiquitin ligase that contains two tryptophan residues 20 to 22 amino acid residues apart (see M. Sudol, Prog Biophys. Molec. Biol. 65: 113-132,1996), and detectably binds to a Smad PY motif, as described herein. Within preferred embodiments, a WW domain satisfies the following consensus sequence:
>
> GPLPXGWEX3tttGtXYYhXHNTtTTtWXtPt (SEQ ID NO: 2)
>
> wherein each t is an independently selected polar amino acid residue (e. g., S, H, P, D, E, T or Y), h is a hydrophobic residue (e.g., I, V, L or M) and X is any amino acid. Within this and other sequences provided herein, amino acid residues are indicated using the standard one-or three-letter code.

(Page 13, lines 15-25). The specification goes on to explain which HECT E3 ubiquitin ligase "variant" embodiments may be used in the claimed methods:

> Within the assays provided herein, a polypeptide comprising a WW domain may be a full length HECT E3 ubiquitin ligase, a portion thereof that comprises a WW domain, or a variant of such a polypeptide in which the WW domain is modified by one or more substitutions, additions, insertions and/or deletions such that the ability of the variant to bind to a Smad PY motif is not substantially diminished (*i.e.*, is enhanced, unchanged or diminished by no more than 10%), relative to the native WW domain sequence. This binding activity may be assessed using a representative binding assay provided herein.

(Page 14, lines 11-17; emphasis added). That is, those variants may be used in which the ability to bind to a Smad PY motif is enhanced, unchanged or diminished by no more than 10%.[1] In addition to the extensive guidance provided above, as well as on, *e.g.*, page 15, lines 13-30, the specification, also includes a non-limiting list of eleven HECT E3 ubiquitin ligase WW domains (SEQ ID NOS: 3-13) that may be used in the claimed methods (*see* page 13, line 26 - page 14, line 10).

Thus, for at least these reasons, Applicants respectfully submit that the claims are fully enabled. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

IV. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has rejected claims 1-10 and 55-56 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, page 10).

---

[1] The Examiner opines that the claims, which recite "is not substantially diminished" and the specification, which defines this phrase as "diminished by no more than 10%" are inaccurate because "diminished and the terms enhanced or unchanged are not synonymous" (Office Action, page 8). However, claim 1 *read in context* is clear. Claim 1 recites, *e.g.*, "a first polypeptide...or a variant thereof...in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase." That is, a first polypeptide may be used, wherein its ability to bind to a Smad protein is either (a) enhanced, (b) unchanged, or (c) diminished by no more than 10% (*i.e.*, "not substantially diminished") relative to the HECT E3 ubiquitin ligase.

Applicants respectfully traverse this ground of rejection.

The Examiner opines that instant specification and claims identify polypeptides comprising a HECT E3 ubiquitin ligase WW domain and Smad PY motif, including variants thereof, but that no conserved domains or structural characteristics are provided for the claimed variants (Office Action, page 10). The Examiner alleges that the skilled "artisan cannot envision the detailed chemical structure of the claimed variant polypeptides, thus, claims reciting said variants lack adequate written description." (Office Action, page 10. The Examiner further opines that the specification "fails to provide any additional representative species of the claimed genus to show that the applicant was in possession of the claimed genus" (Office Action, pages 10-11).

The written description requirement under the first paragraph of 35 U.S.C. § 112 requires the applicant to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Sufficiency of the description is "factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976) *citing In re Ruschig* 379 F.2d 990, 995-96 (C.C.P.A. 1967). Applicants respectfully submit that the specification clearly conveys to one having skill in the art that they were in possession of the claimed invention at the time the application was filed.

As the Examiner is aware, the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. See, *e.g., Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.") A "description of a genus of cDNAs may be achieved by means of... a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *University of California v. Eli Lilly and Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997). Additionally, "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...*i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between

function and structure, or some combination of characteristics." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002) (emphasis added). While the claims recite polypeptides, and not DNA as in *Lilly* and *Enzo*, the same standard applies. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed. Cir. 2004) ("We agree with Rochester that *Fiers*, *Lilly,* and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester's position. It is irrelevant, the statue applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue.")

The claimed methods recite the use of, *e.g.,* a first polypeptide comprising a HECT E3 ubiquitin ligase domain; SEQ ID NOS: 1-13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase. Thus, the claims recite a polypeptide having (1) a HECT E3 WW domain, (2) a specific SEQ ID NO, or (3) a variant thereof.

As discussed in the previous section, the specification defines what constitutes a "HECT E3 WW domain," and includes a number of embodiments:

> A HECT E3 WW domain, as used herein, is a region of a HECT E3 ubiquitin ligase that contains two tryptophan residues 20 to 22 amino acid residues apart (see M. Sudol, Prog Biophys. Molec. Biol. 65: 113-132,1996), and detectably binds to a Smad PY motif, as described herein. Within preferred embodiments, a WW domain satisfies the following consensus sequence:
>
> GPLPXGWEX3tttGtXYYhXHNTtTTtWXtPt (SEQ ID NO: 2)
>
> wherein each t is an independently selected polar amino acid residue (e. g., S, H, P, D, E, T or Y), h is a hydrophobic residue (e.g., I, V, L or M) and X is any amino acid. Within this and other sequences provided herein, amino acid residues are indicated using the standard one-or three-letter code.

(Specification, page 13, lines 15-25). The specification, also includes a non-limiting list of eleven HECT E3 ubiquitin ligase WW domains (SEQ ID NOS: 3-13) that may be used in the claimed methods (*see* page 13, line 26 - page 14, line 10). Thus, the specification has identified a "complete or partial structure," as required by *Enzo*.

Further, the specification discloses that HECT E3 ubiquitin ligases that contain a WW domain bind to a PY motif in certain Smad proteins, resulting in ubiquitination and

proteasome-mediated degradation of the target Smads. That is, the specification discloses "functional characteristics when coupled with a known or disclosed correlation between function and structure," as required by *Enzo*.

Finally, with respect to "variants thereof," the specification goes explains which HECT E3 ubiquitin ligase "variant" embodiments may be used in the claimed methods:

> Within the assays provided herein, a polypeptide comprising a WW domain may be a full length HECT E3 ubiquitin ligase, a portion thereof that comprises a WW domain, or a variant of such a polypeptide in which the WW domain is modified by one or more substitutions, additions, insertions and/or deletions such that the ability of the variant to bind to a Smad PY motif is not substantially diminished (*i.e.*, is enhanced, unchanged or diminished by no more than 10%), relative to the native WW domain sequence. This binding activity may be assessed using a representative binding assay provided herein.

(Page 14, lines 11-17; emphasis added). That is, the specification discloses "functional characteristics when coupled with a known or disclosed correlation between function and structure," as required by *Enzo*.

Thus, for at least these reasons, Applicants submit that the claims comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

V. Non-Statutory Double Patenting

Claims 1 and 4 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 55-60 of co-owned U.S. Serial No. 10/307,956 (Attorney Docket No. 10624-108-999) ("the '956 application") (Office Action, page 13).

Applicants respectfully traverse this ground of rejection.

First, Applicants wish to point out the'956 application is a divisional application of the instant application, and claims 55-60 of the '956 application essentially correlate with withdrawn claims 38-40 of the present application. The claims of the present application were the subject of a 10-way Restriction Requirement by the Examiner on May 23, 2000, and

claims 1-10 were in Group I drawn to methods of screening for modulators of ubiquitin ligase/Smad binding, whereas claims 38-40 were Group IX drawn to methods of inhibiting ubiquitin ligase/Smad binding. As such, the rejection of obviousness-type double patenting is improper (*see* M.P.E.P. § 804 ("Generally, a double patenting rejection is not permitted where the claimed subject matter is presented in a divisional application as a result of a restriction requirement made in a parent application under 35 U.S.C. 121").

That being said, the '956 application has been abandoned for failure to respond to the Office Action dated June 7, 2005. Thus, this ground of rejection is moot.

Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

VI. Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-2, 4, 55 and 56 under 35 U.S.C. § 103 as allegedly being obvious over Pirozzi *et al.* (U.S. Patent No. 6,011,137) ("Pirozzi") "based on the broad recitation of variant thereof" (Office Action, page 15).

Applicants respectfully traverse this ground of rejection.

The Examiner cites Pirozzi as teaching methods and assays to screen compounds that are agonists or antagonists of the interaction of a polypeptide having a WW domain by using a candidate compound, and alleges that it was known in the prior art that the WW domain is involved in cell signaling and growth regulation (Office Action, page 15). The Examiner opines that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Pirozzi teaches a screening method useful for detecting an agonist or antagonist of the WW domain interaction with candidate compounds and the art recognized the involvement of said domain with cell signaling (Office Action, page 16). Thus, the Examiner alleges that if would have been obvious to one of ordinary skill in the art to modify the teachings of Pirozzi to use the interaction of Smad and HECT E3 ubiquitin ligase to screen for effectors of BMP function (*Id.*).

Pirozzi generally discloses assays for the discovery of potential drug candidates that affect the WW domain-containing polypeptide-"recognition unit" interactions (see Section 5.4). However, Applicants submit that nowhere does Pirozzi disclose or suggest (1) *any*

method for screening for an agent that modulates BMP-mediated signaling, *much less* a method for screening for an agent that modulates BMP-mediated signaling comprising contacting (i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain, or variant thereof, in which the ability to bind a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase, (ii) a second polypeptide comprising a Smad PY motif, or variant thereof, in which the ability to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif, and (iii) a candidate agent being screened for its ability to modulate BMP-mediated signaling. While it is true that Pirozzi discloses polypeptides that comprise a PPPPY motif, the Examiner has provided no evidence whatsoever that these PPPPY motif-containing polypeptides are Smad PY motif "variants" as recited in the claims. That is, the Examiner has failed to provide evidence that the Pirozzi PY motif polypeptides are a "10-14 consecutive amino acid portion of a Smad protein that contains a PPxY (Pro-Pro-Xaa-Tyr; SEQ ID NO: 14) sequence" (see, *e.g.,* specification at page 14, line18-21), or a variant thereof, wherein the ability of the variant to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif (see, *e.g.,* specification at page 15, lines 6-11). Indeed, the only PPPPY polypeptides disclosed in Pirozzi are the mouse YAP protein or "peptide recognition units" simply labeled "TP" and "QP" (SEQ ID NOS 6 and 8 at Col. 38, lines 22-26) and WBP-1 and -2A (SEQ ID NOS:9-10 at Col. 39, lines 52-58) There is no evidence that these polypeptides are Smad PY motif "variants," as recited in the claims.

Even assuming *arguendo* that such PPPPY motifs are Smad PY motif "variants," Pirozzi does not make obvious the claimed methods because Pirozzi still fails to disclose methods for screening for an agent that modulates BMP-mediated signaling.

Applicants also disagree with the Examiner's opinion that it would have been obvious to one of ordinary skill in the art to modify the teachings of Pirozzi to use the interaction of Smad and HECT E3 ubiquitin ligase to screen for effectors of BMP function (Office Action, page 16). It is not sufficient that the prior art *can be* modified to produce the claimed invention: the modification is non-obvious unless the prior art suggests the desirability thereof. *In re Laskowski,* 10 USPQ 2d 1397 (Fed. Cir. 1989). Further, the invention as a whole must be considered when determining obviousness, rather than the obviousness of any substitution of modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed.

Cir. 1986). The Examiner has provided no evidence that those skilled in the art were even aware that HECT E3 ubiquitin ligases are binding partners for Smad proteins and/or that HECT E3 ubiquitin ligases and Smad proteins were involved in BMP-mediated signaling. Instead, the Examiner points to the background section of the Applicants' specification that simply states that Smads were known in the art (Office Action, page 16). Without such evidence, Applicants submit that there would be no motivation to substitute the polypeptides recited in the claims into the assays disclosed in Pirozzi.

As discussed in the specification, the present invention is based, in part, on the discovery that signaling mediated by TGF-β family members is dampened by ubiquitin-mediated degradation of certain Smad proteins, and HECT E3 ubiquitin ligases that contain a WW domain bind to a PY motif in certain Smad proteins resulting in ubiquitination and proteasome-mediated degradation of the target Smads (see, *e.g.*, page 9, lines 15-22).

Thus, for at least these reasons, Applicants respectfully submit that the claims are not rendered obvious by Pirozzi. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

VII. Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a three (3) month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith, which extends the response period from February 2, 2005 to May 2, 2006. The Petition further authorizes the PTO to charge the two month extension fee of $1020 to our Deposit Account No. 50-3013. Applicants believe no other fees are due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 50-3013. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition filed concurrently herewith, such an

extension is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

Date: May 2, 2006

Tamera M. Pertmer, Ph.D. (Reg. No. 47,856)
JONES DAY
12750 High Bluff Drive, Suite 300
San Diego, CA 92130
(858) 314-1181

For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, NY 10017-6702
(212) 326-3939